PATENT
Attorney Docket No. 3495.0111-11
Customer Number: 22,852

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#27

In re Application of:

Bernard DUJON et al.

Serial Number: 09/492,697

Filed: January 27, 2000

Group Art Unit: 1636

Examiner: KAUSHAL, S.

For: NUCLEOTIDE SEQUENCE ENCODING THE ENZYME I-*SCE*I AND THE USES THEREOF

MAIL STOP NON-FEE AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE TO PAPER NO. 26

In response to the Office Action dated April 14, 2003 (Paper No. 26), applicants submit the following remarks.

REMARKS

Reconsideration of this application is respectfully requested.

Claims 61-79 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner contends that the specification only teaches SEQ ID NOs: 17, 19, 21, 23, 25, 29, 35, 37, 39, 41, and 43, and fails to disclose any

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other nucleic acid sequences that can be cleaved with I-*Sce*I, I-*Sce*IV, I-*Sce*II, I-*Ceu*I, I-*Ppo*I, I-*Sce*III, I-*Cre*I, I-*Csm*I, I-*Pan*I, I-*Tev*I, I-*Tev*II, and I-*Tev*III. The Examiner concludes that applicants were not in possession of the claimed genus "because a description of only one member of this genus is not representative of the variants of [the] genus and is insufficient to support the claim." (Paper No. 26 at 4.)

Applicants traverse the rejection. Applicants have not simply taught single species. Rather, applicants have taught genera, for example, an I-*Sce*I site, and species within these genera, for example, SEQ ID NO: 17. In reaching the conclusion that applicants do not adequately describe the claimed genera, the Examiner has not considered the express teachings of the specification and the body of knowledge possessed by the skilled artisan at the time that the application was filed. For example, the Examiner has not considered the fact than many additional species of the claimed endonuclease sites, together with techniques for their generation, were known in the art at the time that the application was filed. When these factors are taken into consideration, it is evident that applicants' teachings are sufficient to support the claimed genera.

For example, the specification teaches an 18 base pair recognition sequence for I-*Sce*I. (Specification at 18, lines 20-27.) The specification further teaches that the recognition sequence is partially degenerate, and that some base substitutions result in reduced sensitivity or complete insensitivity to the enzyme, depending upon the position and nature of the substitution. (*Id.* at 19, lines 5-9.) Applicants further provided a compilation of different changes in the recognition

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sequence for I-*Sce*I and the effect of these changes on enzyme activity. (*Id.* at Fig. 3.) There can be no doubt that applicants' specification provides additional species of representative I-*Sce*I recognition sites.

This information is also depicted in Fig. 4 of Colleaux et al., 1988 (Exhibit 1), which is cited on page 51 of the specification. Colleaux et al. indicate that I-*Sce*I recognition sites were generated by construction of randomly mutated recognition sites and tested for enzyme cleavage. Colleaux et al at 6022, col. 2, Materials and Methods. In view of this information, the skilled artisan would understand that applicants had possession of additional species of I-*Sce*I recognition sites beyond the I-*Sce*I recognition site on page 18, and that these species were representative of the claimed genus.

Likewise, applicants disclose other genera, for example, I-*Sce*IV, I-*Sce*II, I-*Ceu*I, I-*Ppo*I, I-*Sce*III, I-*Cre*I, I-*Csm*I, I-*Pan*I, I-*Tev*I, I-*Tev*II, and I-*Tev*III sites, and species within each of these genera, for example, SEQ ID NOs: 17, 19, 21, 23, 25, 29, 35, 37, 39, 41, and 43. Applicants provide herewith Exhibits 2-11 as objective evidence that many other species within these genera beyond the specific SEQ ID NOs provided by applicants were well-known in the art, and as objective evidence that techniques for screening for species with these genera were also well-known in the art at the time the application was filed.

In Sargueil et al., 1990, (Exhibit 2), which is cited on page 26 of the specification, the recognition site of I-*Sce*II was characterized. In Fig. 3, many different I-*Sce*II recognition sites are depicted. Sargueil et al. at 5663. Moreover, Sargueil et al. indicate that I-*Sce*II recognition

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sites were generated by degenerate oligonucleotide synthesis and tested for enzyme cleavage. *Id.* at 5660.

Similarly, in Wernette et al., 1992 (Exhibit 3), the recognition site of I-*Sce*II was characterized. In Table 1 and Fig. 3, many different I-*Sce*II recognition sites are depicted. Wernette et al. at 718. Moreover, Wernette et al. indicate that I-*Sce*II recognition sites were generated by random and site-directed mutagenesis and tested for enzyme cleavage. *Id.* at 717. In view of this information, the skilled artisan would understand that applicants had possession of species of I-*Sce*II recognition sites that were representative of the claimed genus.

In Schapira et al., 1993 (Exhibit 4), the recognition site of I-*Sce*III was characterized. In Fig. 3, many different I-*Sce*III recognition sites are depicted. Schapira et al. at 3686. Moreover, Schapira et al. indicate that I-*Sce*III recognition sites were generated by random mutagenesis and tested for enzyme cleavage. *Id.* at 3684. In view of this information, the skilled artisan would understand that applicants had possession of species of I-*Sce*III recognition sites that were representative of the claimed genus.

In Seraphin et al., 1992 (Exhibit 5), the recognition site of I-*Sce*IV (also known as aI5α intron-encoded endonuclease) was determined. As can be seen in Fig. 5C and as discussed on page 5, col. 2, ¶1, changes in the I-*Sce*IV recognition site are tolerated, especially when they are in the third nucleotide position. In view of this information, the skilled artisan would understand that applicants had possession of species of I-*Sce*IV recognition sites that were representative of the claimed genus.

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In Chu et al., 1991 (Exhibit 6), which is cited on page 26 of the specification, the recognition site of I-*Tev*I was characterized. In Table 1, many different I-*Tev*I recognition sites are depicted. Chu et al. at 6867. Moreover, Chu et al. indicate that I-*Tev*I recognition sites were generated by oligonucleotide-directed mutagenesis and tested for enzyme cleavage. *Id.* at 6864-5.

Similarly, in Bryk et al., 1990, (Exhibit 7), the recognition site of I-*Tev*I was characterized. In Fig. 2, many different I- *Tev*I recognition sites are depicted. Bryk et al. at 2144. Moreover, Bryk et al. indicate that I-*Tev*I recognition sites were generated by selection of sites from a degenerate oligonucleotide pool and tested for enzyme cleavage. *Id.* at 2148-9. In view of this information, the skilled artisan would understand that applicants had possession of species of I-*Tev*I recognition sites that were representative of the claimed genus.

In Bell-Pedersen et al., 1990 (Exhibit 8), which is cited on page 26 of the specification, the recognition site of I-*Tev*II was determined. As can be seen in Fig. 3, and as discussed on page 3767 col. 1, ¶1, extensive heterogeneity in the I-*Tev*II recognition site is tolerated. In view of this information, the skilled artisan would understand that applicants had possession of species of I-*Tev*II recognition sites that were representative of the claimed genus.

In Marshall et al., 1992, (Exhibit 9), the recognition site of I-*Ceu*I was characterized. In Table 1 and Fig. 3, many different I-*Ceu*I recognition sites are depicted. Marshall et al. at 6404. Moreover, Marshall et al. indicate that I-*Ceu*I recognition sites were generated by random and site-directed mutagenesis and tested for enzyme cleavage. *Id.* at 6402. In view of this

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information, the skilled artisan would understand that applicants had possession of species of I-*Ceu*I recognition sites that were representative of the claimed genus.

In Ellison et al., 1993, (Exhibit 10), the recognition site of I-*Ppo*I was characterized. Ellison et al. indicate that I-*Ppo*I tolerates changes within its binding site, and that most oligonucleotides containing single substitutions within the recognition sequence are cleaved to the same extent as oligonucleotides containing wild-type sequences. Ellison et al. at 7536. Ellison et al. further indicate that, while several oligonucleotides containing two substituted bases resulted in severely reduced cutting by I-*Ppo*I, other doubly-substituted oligonucleotides were cleaved at levels similar to the wild-type sequence. *Id.* In view of this information, the skilled artisan would understand that applicants had possession of species of I-*Ppo*I recognition sites that were representative of the claimed genus.

In Durrenberger et al., 1993, (Exhibit 11), the recognition site of I-*Cre*I was characterized. In Fig. 3, many different I-*Cre*I recognition sites are depicted. Durrenberger et al. at 412. Durrenberger et al. indicate that I-*Cre*I tolerates single and even multiple base changes within its recognition sequence. *Id.* at 413. In view of this information, the skilled artisan would understand that applicants had possession of species of I-*Cre*I recognition sites that were representative of the claimed genus.

Furthermore, using the techniques disclosed in the above references, the skilled artisan would have been able to envision and generate many species of recognition sites, which would be representative of the claimed genera, based on the recognition sites disclosed in applicants'

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specification and recognition sites that were known in the art. Coupled with what was well-known in the art, applicants' teachings of the claimed genera and species within each of these genera suffices to fulfill the written description requirement for the claimed invention. Accordingly, applicants respectfully request withdrawal of the rejection.

Claims 61-79 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not providing enablement for any transgenic mouse or cell thereof that comprises a nucleic acid sequence other than SEQ ID NOs: 17, 19, 21, 23, 25, 29, 35, 37, 39, 41, and 43 cleaved by I-*Sce*I, I-*Sce*IV, I-*Sce*II, I-*Ceu*I, I-*Ppo*I, I-*Sce*III, I-*Cre*I, I-*Csm*I, I-*Pan*I, I-*Tev*I, I-*Tev*II, or I-*Tev*III endonucleases. The Examiner bases this conclusion on a belief that that the specification fails to disclose any nucleic acid sequences other than those identified by the above sequence identification numbers.

Applicants traverse the rejection. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988). As discussed above, the Examiner has not considered the express teachings of the specification and the body of knowledge possessed by the skilled artisan at the time that the application was filed. For example, the Examiner has not considered the fact than many additional species of the claimed endonuclease sites, together with techniques for their generation, were known in the art at the time that the application was filed. When these

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factors are considered, it is apparent that the Examiner's basis for the rejection is in error, and that applicants' claims fulfill the enablement requirement of 35 U.SC. § 112, first paragraph.

As discussed above, applicants teach that the I-*Sce*I recognition sequence is partially degenerate, and that some base substitutions result in reduced sensitivity or complete insensitivity to the enzyme, depending upon the position and nature of the substitution. (Specification at 19, lines 5-9.) Applicants further provided a compilation of different changes in the recognition sequence for I-*Sce*I and the effect of these changes on enzyme activity. (*Id.* at Fig. 3) There can be no doubt that applicants' specification provides additional species of I-*Sce*I recognition sites.

Moreover, Exhibits 1-11 provide objective evidence that many other species of the claimed recognition sites, beyond the specific SEQ ID NOs provided by applicants, were well-known in the art. Exhibits 1-11 also provide objective evidence that techniques for screening for species within these genera were also well-known in the art at the time the application was filed. Accordingly, no undue experimentation would be required to practice applicants' claimed invention.

Furthermore, the Examiner's allegation that "the specification cannot be relied upon to teach how to make the variants as claimed" is in error. Applicants' specification specifically cites, and incorporates by reference, Colleaux et al., 1988 (Exhibit 1); Sargueil et al., 1990, (Exhibit 2); and Chu et al., 1991 (Exhibit 6). Each of these references discloses techniques for making the claimed variants. As a result, the specification can be relied upon to teach how to

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make the variants as claimed. Accordingly, applicants respectfully request withdrawal of the rejection.

Applicants respectfully submit that the application is in condition for allowance, and respectfully request issuance of a notice of allowance. If the Examiner should disagree, he is invited to contact the undersigned to discuss any remaining issues.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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By: _____

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